REMARKS

Introductory Comments:

Claims 1-8, 10, 11, 13-16, 18, 19, 21-30, 32, 33, 35-42, 44, 45 and 47-55 are pending in the application. Claims 1-6 and 50-55 have been withdrawn from further consideration pursuant to 37 C.F.R. § 1.142(b) as drawn to a non-elected invention. Applicants note with appreciation that the Office has withdrawn the following objections and/or rejections to the claims: **(a)** the objection to claims 7, 8, 10, 11, 13-16, 18, 19, 21-30, 32, 33, 35-42, 44, 45 and 47-49 as informal; **(b)** the rejection of claims 37-42, 44, 45 and 47-49 under 35 U.S.C. §112, second paragraph; **(c)** the rejection of claims 13, 14, 21, 22, 35, 36, 47 and 48 under 35 U.S.C. §112, second paragraph; **(d)** the rejection of claims 7, 8, 10, 11, 13-16, 18, 19, 21-30, 32, 33, 35-42, 44, 45 and 47-49 under 35 U.S.C. §112, first paragraph; and **(e)** the rejection of claims 7, 8, 10, 11, 13-16, 18, 19, 21-30, 32, 33, 35-42, 44, 45 and 47-49 under 35 U.S.C. §112, first paragraph.

However, the Office has maintained the following objections and/or rejections to the claims: **(1)** claim 26 is objected on the basis of informality; **(2)** claims 8, 16, 30, and 42 remain rejected under 35 U.S.C. § 112, second paragraph, as indefinite; **(3)** claims 7, 8, 10, 11, 13-16, 18, 19, 21-30, 32, 33, 35-42, 44, 45 and 47-49 remain rejected under 35 U.S.C. §112, first paragraph, as nonenabled; **(4)** claims 8, 10, 11, 13, 16, 18, 19, 21, 30, 32, 33, 35, 42, 44, 45 and 47 remain rejected under 35 U.S.C. § 112, first paragraph, as nonenabled; **(5)** claims 7, 8, 10, 11, 15, 16, 18 and 19 remain rejected under 35 U.S.C. §103(a) as unpatentable over Lowrie et al. (1997) *Vaccine* 15(8):834-838 ("Lowrie"); and **(6)** claims 23, 25-30, 32, 33, 37-42, 44 and 45 remain rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Lowrie in

view of U.S. Patent No. 5,100,792 to Sanford et al. ("Sanford"). All remaining objections and/or rejections to the claims are traversed for the following reasons.

Overview of the Amendment:

Applicants, by way of this response, have entered amendments to claims 8, 16, 26, 30 and 42 in order to recite the invention with greater particularity. For example, claim 26 has been amended to remove the single bracket mistakenly left in the clean copy of the claim submitted with the response dated 20 May 2002. Claims 8, 16, 30 and 42 have merely been amended to recite that the secondary composition contains either a nucleic acid molecule encoding the *Mycobacterium tuberculosis* antigen, or the antigens in peptide or protein form. Support for these amendments can be found throughout the specification as originally filed, particularly at page 30, lines 1-11. Accordingly, no new matter has been added by way of these claim amendments, and the entry thereof is respectfully requested.

Pursuant to the Revised Notice from the USPTO, dated 13 February 2003, and entitled "Amendments May Now Be Submitted In Revised Format," the subject amendment has not been provided in both "clean version" and in "marked-up version" in conformance with 37 C.F.R. §1.121(b)(1) parts (ii) and (iii). Instead, this Preliminary Amendment includes a complete listing of all claims in the present application with an indication of the current status of each. The listing begins on a separate sheet and is captioned "CURRENT STATUS OF ALL CLAIMS IN THE APPLICATION".

The Objection to the Claims:

The Office has objected that claim 26 remains informal on the basis of a typographical error appearing in the clean copy of that claim as submitted with the

Response filed 20 May 2002. Correction was required. Applicants draw the Office's attention to the amendment to claim 26, wherein the subject bracket has been deleted from the claim. Reconsideration and withdrawal of the objection to claim 26 is thus respectfully requested.

The Rejection under 35 U.S.C. §112, second paragraph:

Claims 8, 16, 30 and 42 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite. In particular, the Office has objected that the "secondary composition" recited therein is indefinite on the basis that such composition "is not defined." Office Action at page 5.

In response, applicants draw the Office's attention tot he amendments to claims 8, 16, 30 and 42 submitted herewith, wherein the secondary compositions have been expressly defined in the claims. Applicants submit that the subject amendments are sufficient to overcome the subject rejection. Reconsideration and withdrawal of the rejection of claims 8, 16, 30 and 42 under 35 U.S.C. §112, second paragraph, is thus respectfully requested.

The rejections under 35 U.S.C. §112, first paragraph:

Claims 7, 8, 10, 11, 13-16, 18, 19, 21-30, 32, 33, 35-42, 44, 45 and 47-49 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled, wherein the Office has continued to refuse to accept that the skilled artisan would view the guinea pig model as reasonably predictive of success in humans. In particular, the Office asserts "the filed of tuberculosis is a unique example in animal/human studies in that the use of animal models to predict success in humans has been universally unsuccessful except for the one example, BCG." Office Action at page 5. Applicants respectfully traverse the rejection.

Initially, it appears that the Office has relied upon personal knowledge in order to support the instant rejection, where the Office asserts that animal models are universally unsuccessful in the field of tuberculosis, but the Office has not submitted any evidence in support of this sweeping assertion. If the Office is indeed in possession of such knowledge, applicants request that the Office provide a declaration documenting the basis for this assertion such that applicants can review the evidence and respond accordingly. In the absence of such documentary support, the rejection must fall.

However, notwithstanding the above, applicants note that the Office does acknowledge that the guinea pig model is indeed predictive of human results in the case of BCG. Office Action at page 5. The BCG vaccine is currently the only registered vaccine available for human administration, and as such it is the "Gold Standard" for tuberculosis vaccines. Applicants recognized that BCG is the Gold Standard for tuberculosis vaccines (see applicants' specification at page 34, line 14) at the time of filing their application. Consequently, applicants used the BCG vaccine as a positive control in comparative studies in order to gauge the efficacy of their recited vaccine compositions in eliciting a meaningful immune response, using a number of well-established success criteria to establish the efficacy of the experimental vaccine compositions. In this regard, successful practice of applicants' recited methods of nucleic acid immunization includes therapeutic endpoints such as diminishing the duration and/or severity of disease, increasing survival rates, as well as prevention of infection. Applicants respectfully submit that if their recited vaccines performed to the same standard as BCG in eliciting a meaningful immune response in the subject comparative studies, then there is no reason whatsoever to doubt that applicants' recited vaccines would likewise be efficacious in humans, and their claims are therefore properly enabled.

Applicants thus draw the Office's attention to the working examples provided at pages 30-40 of the specification, wherein the comparative data clearly support the efficacy of applicants' recited vaccines. The groups studied by the applicants are summarized as follows: GROUP A (DNA encoding 85A antigen); GROUP B (DNA encoding 85A and MPT32 antigen); GROUP Ca (DNA encoding cocktail of 10 antigens); GROUP Cb (prime with DNA encoding cocktail of 10 antigens and boost with BCG); GROUP D (negative control); and GROUP E (BCG positive control). As can be seen in the data presented in Tables 3 and 4, 20% of all five test groups (GROUP D, negative control excluded) were protected from dissemination of bacilli from the lungs to the spleen. Accordingly, all five test groups performed equally as well as the Gold Standard, BCG. In addition, when looking at GROUP Cb and the BCG positive control, it can be seen that these two vaccines demonstrated identical results with reduced pathology in the lungs and spleens relative to the GROUP D negative controls. In this regard, as shown in Table 2, 100% of the GROUP Cb animals and 100% of the GROUP E animals had Grade I splenic lesions (mild to moderate splenitis). In addition, the GROUP Cb animals exhibited reduced lung pathology relative to the GROUP E (BCG Gold Standard). This can be seen by reviewing the data presented in Table 1, where 50% of the test subjects (animals 410 and 458) in the GROUP Cb animals had mild to moderate Grade I lung lesions while only 20% of the test subjects (animal number 422) in the five GROUP E animals had Grade I lung lesions. It is also quite notable that 60% of the GROUP E (BCG) test animals had Grade II lung lesions, and the final 20% had Grade III lung lesions. Finally, the survival rates seen with the GROUP Cb and GROUP E animals were substantially identical (80% and 100%, respectively).

Accordingly, in all three of these key areas, applicants recited vaccine compositions performed as well as or better than the BCG positive controls. These

results were seen in the animal model system that the Office has acknowledged established the link between clinical efficacy in guinea pigs and humans for BCG. There is no reasonable basis for disputing applicants' enabling disclosure on the basis of the reported guinea pig data. The skilled artisan understood that BCG had been tested through the guinea pig animal model system, and could compare in direct head-to-head studies the activity of applicants' recited compositions against BCG. The fact that applicants' vaccines out-performed the Gold Standard BCG vaccine in the art-accepted animal model system would lead the skilled artisan to assume that the same or similar results would be seen in moving to other animal subjects including humans. This is because the determination of enablement is always judged by the standards of those skilled in the art. Applicants submit that, given the level of skill in the art, the detailed description provided by the specification, and the numerous working examples, a skilled artisan could readily practice the claimed invention without undue experimentation. See, e.g., *Utter v. Hiraga*, 6 USPQ2d 1709, 1714 (Fed. Cir. 1988), and *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986).

For all of the foregoing reasons, then, the rejection of claims 7, 8, 10, 11, 13-16, 18, 19, 21-30, 32, 33, 35-42, 44, 45 and 47-49 under 35 U.S.C. §112, first paragraph, is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 8, 10, 11, 13, 16, 18, 19, 21, 30, 32, 33, 35, 42, 44, 45 and 47 stand rejected under 35 U.S.C. §112, first paragraph, as nonenabled. Here, the Office objects that the scope of claims 8, 16, 30 and 42 read on secondary compositions with no requirement that [the same] comprise any of the initial *M. tuberculosis* antigens." Office Action at page 6. The other rejected claims are objected to as reading on the

secondary compositions that do not comprise any of the initial *M. tuberculosis* antigens.

In response, applicants draw the Office's attention the amendments to claims 8, 16, 30 and 42 tendered herewith, wherein the secondary compositions have been expressly defined as containing the initial antigens. Accordingly, applicants submit that the instant rejection has been rendered moot on the basis of the present amendments. Reconsideration and withdrawal of the rejection of claims 8, 10, 11, 13, 16, 18, 19, 21, 30, 32, 33, 35, 42, 44, 45 and 47 under 35 U.S.C. §112, first paragraph, is respectfully requested.

The Rejections under 35 U.S.C. §103(a):

Claims 7, 8, 10, 11, 15, 16, 18 and 19 remain rejected under 35 U.S.C. §103(a) as unpatentable over Lowrie. In particular, the Office asserts that an off-hand comment provided at the top of page 837 of Lowrie is sufficient to render obvious applicants claims to multiple-antigen nucleic acid immunization methods (claim 7), multiple-antigen nucleic acid immunization methods coupled with administration of certain secondary compositions (claim 8), multiple-antigen nucleic acid immunization methods coupled with administration of a culture filtrate protein in a secondary composition, or a subunit thereof (claims 10 and 11), multiple-antigen and multiple-construct nucleic acid immunization methods (claim 15), multiple-antigen and multiple-construct nucleic acid immunization methods coupled with administration of certain secondary compositions (claim 16), and multiple-antigen and multiple-construct nucleic acid immunization methods coupled with administration of a culture filtrate protein in a secondary composition, or a subunit thereof (claims 18 and 19). The sole basis for this rejection is the following sentence "a vaccine that gives protection equal to BCG by endogenous expression of only a few proteins will leave

the majority of the species specific antigens available for diagnostic tests." The Office concludes that this, in of itself, is sufficient to render obvious all of the above-recited methods. Applicants respectfully traverse.

There are three basic requirements for *prima facie* obviousness: (1) there must be some suggestion or motivation to modify or combine the references; (2) there must be a reasonable expectation of success for the modification and/or combination; and (3) the prior art reference must teach or suggest all the claim limitations. When assessing these issues, (a) the claimed invention must be considered as a whole; (b) the references must be considered as a whole and must suggest the desirability of making the combination; (c) the references must be viewed without the benefit of impermissible hindsight; and (d) a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that the Office has failed to satisfy these criteria, and has thus failed to establish *prima facie* obviousness over Lowrie.

Accordingly, Lowrie must be considered as a whole and must suggest the desirability of making applicants' recited combination. Lowrie describes 5 different single antigen DNA vaccines. Lowrie is completely silent with respect to providing a DNA vaccine composition containing multiple tuberculosis antigens. Lowrie never once considered the use of primary and secondary vaccine compositions. Not once did Lowrie discuss or contemplate combining a multiple antigen DNA vaccine approach with secondary compositions containing culture filtrate protein antigens. The sole basis for the Office's rejection is that an entirely vague and indefinite sentence could possibly, if read with the benefit of applicants' teaching, somehow suggest a DNA vaccine composition encoding multiple antigens. The Office does not provide a rationale to support its assertion that this hindsight construction could further lead to methods combining multiple antigen DNA vaccines with applicants'

recited secondary vaccine compositions. Thus, when Lowrie is considered as a whole, it fails to suggest the desirability of making applicants' recited combinations. The ambiguous statement from Lowrie simply does not teach or suggest all of applicants' claim limitations!

In addition, Lowrie cannot be considered to enable applicants' recited combinations. Lowrie fails to teach or even so much as suggest applicants' combinations, and thus cannot be said to enable those combinations. How can one enable that which is not taught or suggested? Accordingly, when Lowrie is considered as a whole, as it must be, and viewed under the reasonable expectation of success standard, again as it must be, it is clear that Lowrie fails to render applicants' recited compositions obvious.

As applicants have already discussed in their previous response, even though it would have been, in theory, perfectly possible for Lowrie et al to combine two or more antigens in their study, they neither did this nor suggested that this should be done. The document is entirely silent on the idea of providing a vaccine composition containing multiple tuberculosis antigens. In fact, Lowrie showed that numerous single antigen vaccines provided "significant protection." Accordingly, this showing would suggest an entirely opposite and perhaps more plausible interpretation of the Office's cited sentence, where Lowrie et al. are suggesting that a number of different antigen systems could be used to vaccinate different individuals in a population, facilitating broad spectrum diagnostic testing in the vaccinated population. Given that there are multiple possible hindsight reconstructions of this single sentence from Lowrie, and that this vague sentence cannot possibly be read to teach or suggest applicants's methods using their recited secondary compositions, Lowrie simply does not rise to the level of a *prima facie* showing of obviousness.

For all of the foregoing reasons, then, the rejection of claims 7, 8, 10, 11, 15, 16, 18 and 19 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 23, 25-30, 32, 33, 37-42, 44 and 45 remain rejected under 35 U.S.C. §103(a) as unpatentable over the combination of Lowrie in view of Sanford. Here again, the sole basis for the Office's rejection is the single sentence discussed herein above. Office Action at page 8. Applicants respectfully traverse.

As discussed above, the primary reference to Lowrie fails to teach or suggest applicants' recited multiple antigen constructs. The secondary reference to Sanford does not provide the missing teaching or suggestion. Accordingly, the Office has failed to establish a *prima facie* showing of obviousness over its proposed combination since the combination and each component thereof fails to teach or suggest all of applicants' recited claim limitations. Accordingly, the rejection of claims 23, 25-30, 32, 33, 37-42, 44 and 45 under 35 U.S.C. §103(a) is improper. Reconsideration and withdrawal is thus respectfully requested.

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CONCLUSION

Applicants respectfully submit that the claims as now pending define an invention which complies with the requirements of 35 U.S.C. § 112 and which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order and an early notification to that effect is earnestly solicited. Applicants further ask that, should the Examiner note any minor remaining issues that may be resolved with a telephone call, that he contact the undersigned in the UK at +44 1865 332 600.

Respectfully submitted,

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